From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/005996	03.06.2004	04.06.2003

International Patent Classification (IPC) or both national classification and IPC
A61K35/14, A61K35/26, A61K35/66, A61K38/21, A61P31/00, A61P33/00, A61P35/00, A61P37/00

Applicant
GESELLSCHAFT FUR BIOTECHNOLOGISCHE FORSCHUNG MBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
EP-A-1 382 352	2004-01-21	2002-07-19	

Re Item VII
Certain defects in the international application

The reference "Weigt et al" on page 2, par. 4 is not correctly cited (pages).

Re Item VIII
Certain observations on the international application

1. The application does not meet the requirements of Article 6 PCT, because claim 1 is not clear since the comprised step of culturing DCs would be of no relevance in the case only lymphocytes are contained in the composition. This objection can be overcome by inserting "cocultivated with said dendritic cells" after the word "lymphocytes" (as already cited in claim 10).

2. Claim 23 dependent on claims 16-18 being product and not "method of treatment" claims also is not clear in this regard.

The solution proposed in these claims can be considered as involving an inventive step (Articles 52(1) and 56 EPC) for the following reasons:

Culturing DCs with various stimuli such as TLR agonists or interferons is already known (D1, D3, D4). There are many possible options as to the combination of specific stimuli, and the feature "one IFNgamma receptor agonist and at least one TLR 2 and/or 6 agonist" is one of these. The skilled person could have choosen this combination but as well as many others in order to solve the problem posed.
Since synergistic effects for this combination have been shown in the description which were not expected, inventive step can be acknowledged.

In regard to independent claims 16 and 19, the following has to be remarked:

The synergistic effect of IFN beta or gamma and TLR 2 or 6 agonists on induction of macrophages has been clearly shown in D5 in order to induce maximal levels of NO secretion as well as iNOS gene expression (being one of the proinflammatory genes activated). Macrophages play a central role in host defense, hence the skilled in the art would try the tested combinations in order to stimulate macrophages for using them in immunostimulation.
As already stated above, the skilled person would also have many other possibilities in order to achieve macrophage stimulation. Furthermore, synergistic effects in improvement of lung function have been shown in airflow obstructed mice for the combination MALP-2 and IFN-gamma by the applicant.
Therefore, inventive step can be acknowledged for claims 16-23 as well.

4. For the assessment of the present claims 11-14 and 19-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

responses. DC vaccination appears to be safe and is thought of being a method of choice for treating tumor-bearing patients in the long run (p. 139-140; p. 143, col. 2).

Likewise, D2 disclose the stimulation of DCs such as by pathogen-derived products and the development of Th1 cells when appropriately stimulated (p. 101-102).

D3 claims a process for culturing DCs for 4-6 days whereby TNF-alpha as well as IFN-gamma as a further possibility are added (claim 1; ex. 7).

D4 claims antigen-presenting cells subjected to at least one of specific treatments mentioned such as in vitro incubation of immature dendritic cells with allogenic lymphocytes and/or treatment with interferon (alpha, beta or gamma). The cells are being used for reducing allologous immune reactions, i.e. suppress graft versus host responses (claims).

Since no document discloses the use of dendritic cells (with or without lymphocytes) which have been cultivated with an INF-gamma agonist and a TLR 2 or 6 agonist, claims 1-15 and 19-23 are novel, in the case the clarity objection is met (see VIII).

D5 showing the simultaneous stimulation of macrophages by IFN gamma and TLR 2 agonists such as S-[2,3-bis-(palmitoyloxy)-2-RS)-propyl]-N-palmitoyl-(R)-Cys-(S)-Ser-Lys4-OH does not show a use of this combination for culturing dendritic cells but the enhancement of NO production (p. 5875, col. 1 - p. 5876, col. 2).
However, the subject-matter of claims 16-18 can be regarded as novel since D5 does not disclose a "pharmaceutical composition" per se.

Hence, claims 1-23 are novel.

3. Inventive step

The problem to be solved by the present invention may be regarded as finding an alternative to the prior art in the treatment of cancer immunotherapy as well as for reducing immune reactions such as graft versus host reactions in transplantation, namely by the use of dentritic cells.

For novel independent claims 1, 10-13, and 15, the following applies:

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 11 and 19-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: SCHULER G ET AL: "The use of dendritic cells in cancer immunotherapy" CURRENT OPINION IN IMMUNOLOGY, CURRENT BIOLOGY LTD. LONDON, GB, vol. 15, no. 2, April 2003 (2003-04), pages 138-147, XP004414291 ISSN: 0952-7915

D2: BOONSTRA ANDRE ET AL: "Flexibility of mouse classical and plasmacytoid-derived dendritic cells in directing T helper type 1 and 2 cell development: Dependency on antigen dose and differential Toll-like receptor ligation." JOURNAL OF EXPERIMENTAL MEDICINE, vol. 197, no. 1, 6 January 2003 (2003-01-06), pages 101-109, XP002256542 ISSN: 0022-1007

D3: FR-A-2 796 961 (CT HOSPITALIER UNIVERSITAIRE D) 2 February 2001 (2001-02-02)

D4: EP-A-1 291 414 (GENETHOR GMBH) 12 March 2003 (2003-03-12)

D5: SCHILLING, DAGMAR ET AL: "Toll-like receptor 4 and Toll-IL-1 receptor domain-containing adapter protein (TIRAP)/myeloid differentiation protein 88 adapter-like (Mal) contribute to maximal IL-6 expression in macrophages" JOURNAL OF IMMUNOLOGY , 169(10), 5874-5880 CODEN: JOIMA3; ISSN: 0022-1767, 2002, XP002296565

2. Novelty

D1 discloses DC vaccination: monocyte-derived dentritic cells are differentiated by exposure to various stimuli such as Toll-like receptor (TLR) ligands inducing eg Th1

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-23
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-10,12-18
	No:	Claims	-

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11, 19-23 in regard to industrial applicability

because:

☒ the said international application, or the said claims Nos. 11, 19-23 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments: